

CARDIOVASCULAR MEDICINE

Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population

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Objective: To evaluate N-terminal pro-brain natriuretic peptide (NT-proBNP) as a diagnostic and prognostic marker for systolic heart failure in the general population.

Design: Study participants, randomly selected to be representative of the background population, filled in a heart failure questionnaire and underwent pulse and blood pressure measurements, electrocardiography, echocardiography, and blood sampling and were followed up for a median (range) period of 805 (60-1171) days.

Setting: Participants were recruited from four randomly selected general practitioners and were examined in a Copenhagen university hospital.

Patients: 382 women and 290 men in four age groups (50-59 (n = 174); 60-69 (n = 204); 70-79 (n = 174); ≥ 80 years (n = 120)).

Main outcome measures: Value of NT-proBNP in evaluating patients with symptoms of heart failure and impaired left ventricular (LV) systolic function; prognostic value of NT-proBNP for mortality and hospital admissions.

Results: In 38 (5.6%) participants LV ejection fraction (LVEF) was ≤ 40%. NT-proBNP identified patients with symptoms of heart failure and LVEF ≤ 40% with a sensitivity of 0.92, a specificity of 0.86, positive and negative predictive values of 0.11 and 1.00, and area under the curve of 0.94. NT-proBNP was the strongest independent predictor of mortality (hazard ratio (HR) = 5.70, p < 0.0001), hospital admissions for heart failure (HR = 13.83, p < 0.0001), and other cardiac admissions (HR = 3.69, p < 0.0001). Mortality (26 v 6, p = 0.0003), heart failure admissions (18 v 2, p = 0.0002), and admissions for other cardiac causes (44 v 13, p < 0.0001) were significantly higher in patients with NT-proBNP above the study median (32.5 pmol/l).

Conclusions: Measurement of NT-proBNP may be useful as a screening tool for systolic heart failure in the general population.

Until recently, heart failure has been a much neglected condition, probably resulting from a combination of lack of good epidemiological data, lack of simple diagnostic techniques, and lack of effective treatment. However, within the past few years, a large amount of epidemiological data has been presented,¹⁻⁴ indicating that heart failure is a common, underdiagnosed, and serious condition with a dismal prognosis, comparable with several forms of cancer.⁵ In the same period, effective treatments for heart failure have become available, including angiotensin converting enzyme inhibitors,⁶ β blockers,⁷ and spironolactone,⁸ creating a need for effective screening tools for the disease. However, diagnosis of heart failure still relies mainly on clinical evaluation and an echocardiographic measure of left ventricular (LV) systolic function.⁹ In an attempt to facilitate and improve diagnosis, biochemical substances have been suggested as alternative markers for the disease. Efforts have focused on the natriuretic peptides, among which brain natriuretic peptide (BNP)¹⁰⁻¹¹ and its amino terminal portion N-terminal pro-brain natriuretic peptide (NT-proBNP),¹² which may hold advantages because of its greater stability,¹³ have proved especially promising. Concentrations of BNP and NT-proBNP are related to LV filling pressures¹⁴ and wall stress.¹⁵ In previous population based studies by McDonagh and colleagues, BNP has been

identified as a promising prognostic¹⁶ and diagnostic marker for impaired LV systolic function.¹⁷ However, community based diagnostic or prognostic heart failure data on NT-proBNP are completely lacking.

The purpose of our study was to evaluate NT-proBNP as a diagnostic marker for systolic heart failure and as a prognostic marker for mortality and cardiac morbidity in a large age controlled sample of the general population.

METHODS

Patients

The study population was recruited from four Copenhagen general practitioners located in the same urban area. The only inclusion criterion was age between 50 and 90 years. Exclusion criteria were inability to cooperate (for example, for mental reasons such as dementia), residency in nursing homes, and lack of response to two written invitations.

Abbreviations: AUC, area under the curve; BNP, brain natriuretic peptide; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristic

Study design

To have a sufficient number of elderly participants, the study sample was stratified to have at least 120 people in each decade. An invitation to participate in the study was sent to all people between 50 and 90 years of age assigned to the first two general practitioners. From the third practice all those aged 60–90 years and from the last practice all those aged 80–90 years were invited. Seventy per cent of those invited participated in the study. The attendance was higher among younger invitees, approximately 75%, and was about 50% in the oldest decade. The study was designed to be representative of the background population in Copenhagen by compensating for the lower response rate in the older age groups through oversampling in these groups. Participants from general practitioners 1 and 2 entered the study in the autumn of 1997 and were submitted to a questionnaire, an echocardiogram, and a blood pressure measurement. They were recalled by the autumn of 1998 ($n = 424$), when an ECG was recorded and their blood sampled. Patients from general practitioner 3 ($n = 207$) and general practitioner 4 ($n = 41$) were submitted to all examinations in the autumn and winter 1998/99. Thus, all patients in the study were effectively examined once. The local ethics committee approved the study and the patients gave written informed consent.

Heart failure questionnaire

All subjects filled in a heart failure questionnaire on medical history, symptoms, drug history, and alcohol and tobacco consumption. Symptoms of heart failure were recorded from questions on ankle swelling and breathlessness (self reported). The degree of breathlessness was recorded from the questionnaire according to the World Health Organization classification (grade 1, no dyspnoea; grade 2, dyspnoea on vacuum cleaning or climbing stairs to the second floor; grade 3, dyspnoea when walking on an even road; grade 4, dyspnoea with minimum exertion; grade 5, orthopnoea; grade 6, dyspnoea at rest).¹⁷ Self reported medical history was recorded from questions on hospital admissions (with special emphasis on admissions for heart failure, pulmonary oedema, and myocardial infarction), history of ischaemic heart disease (previous myocardial infarction, angina, or both), and history of hypertension and diabetes mellitus (insulin or non-insulin treated). Each questionnaire was evaluated immediately after completion and in case of any omissions or inconsistencies, the patients were contacted by telephone to ensure the highest possible quality of the data.

Measurements

Heart rate and blood pressure were measured and a 12 lead standard ECG was recorded and evaluated according to the Minnesota code.¹⁸ From predefined criteria (absence of arrhythmias, ST deviations, Q waves, hypertrophy, and abnormal LV axis), each ECG was classified as either normal or abnormal.

Furthermore, all participants underwent apical four and two chamber and apical long axis two dimensional echocardiography. LV systolic function was evaluated off-line in a blinded fashion by two experienced and independent observers by 16 segment wall motion score index. Normal investigations obtained a wall motion score of 2.0. By multiplying the wall motion score by 30, LV ejection fraction (LVEF) was calculated.¹⁹ Consequently $LVEF \leq 55\%$ reflects abnormal wall motion. LVEF was determined as the average value obtained by the two observers.

Finally, blood samples were collected for determination of biochemical markers. Plasma concentrations of NT-proBNP were measured by a novel, highly sensitive and specific immunoassay based on a sandwich format with unextracted EDTA plasma. The sensitivity of the assay was < 3.0 pmol/l

and the intra-assay and inter-assay coefficients of variation were 1.3% and 4.8%, respectively.²⁰

Mortality data were obtained from the Danish Central Personal Register, which registers all deaths in Denmark within two weeks. Data on admissions for heart failure and other major cardiovascular diseases were extracted from the National Danish Patient Register based on the discharge diagnosis classified according to the *International classification of diseases*, 10th revision (ICD-10).²¹ Heart failure admissions were defined as a primary discharge diagnosis of I50 and other major cardiovascular diseases were defined as I10–I15, I20–I25, I34–I36, I42.1–2,6–9, I46, and I49.9.

Statistical analysis

Normal data distribution was verified with histograms and normal plots. The plasma concentration of NT-proBNP had a log normal distribution and was consequently logarithmically (\log_{10}) transformed. Two-sample t tests between mean values of variables in groups with and without systolic heart failure were performed in case of normal distribution of data; alternatively Mann-Whitney tests were used. Dichotomous data were analysed by continuity adjusted χ^2 tests. Plasma concentrations of NT-proBNP in different systolic heart failure groups were compared by analysis of variance. Potential markers for the diagnosis of systolic heart failure were analysed by multiple logistic regression analysis with backward elimination. Subsequently, receiver operating characteristic (ROC) curves for the ability of NT-proBNP to detect systolic dysfunction, as well as to diagnose systolic heart failure, were calculated. The optimum combination of sensitivity and specificity, defined as the point on the ROC curve closest to the upper left corner of the diagram, were derived together with the area under the curve (AUC). The ROC curve derived optimum NT-proBNP cut point concentration was subsequently used to calculate positive and negative predictive values. Potential independent prognostic markers for mortality, congestive heart failure admissions, and other cardiac admissions were evaluated by Cox proportional hazards analyses (time to first event). The study population was divided in two by the median NT-proBNP concentration. Kaplan-Meier curves for total mortality, congestive heart failure admissions, and other cardiac admissions were calculated in the two groups and differences between groups were assessed with the log rank test. All tests were two sided and a significance level of 5% was used. All tests were done with SAS (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Demographic data

Table 1 gives demographic and clinical characteristics, as well as fundamental measurements.

When comparing our study population with the background population of Copenhagen, there was no evidence of sex difference in sampling (Mantel-Haenszel male to female proportion (over the four ages groups) was 1.1 (NS)) and no evidence of heterogeneity over age groups (NS).

There was no difference in admission rates before sampling between the total invited sample and the background population (NS), nor was there any difference within the total invited sample between participants and non-participants (NS). During the year after sampling, the admission rate was significantly increased for the total invited sample ($p = 0.03$) with no significant difference between participants and non-participants (NS).

The participants had a one year mortality very close to that of the background population, whereas non-participants had a more than three times higher one year mortality than the participants ($p < 0.001$).

Table 1 Baseline characteristics and drug treatment

Characteristics	
Demographic data	
Male/female	290 (43%)/382 (57%)
Age (years)	
50–59	174 (26%)
60–69	204 (30%)
70–79	174 (26%)
≥ 80	120 (18%)
Median (range)	68.1 (51.2–91.3)
Current daily smoker	237 (35%)
Clinical history	
Dyspnoea grade*	
2	84 (13%)
3	51 (8%)
4	47 (7%)
5	14 (2%)
6	23 (3%)
Total	219 (33%)
Ankle oedema	155 (23%)
Ischaemic heart disease	96 (14%)
Hypertension	169 (25%)
Angina	83 (12%)
Diabetes mellitus	
Insulin treated	7 (1%)
Non-insulin treated	36 (5%)
Measurements	
Atrial fibrillation	24 (4%)
Heart rate (beats/min)	75.4 (13.4)
Systolic blood pressure (mm Hg)	144 (23.2)
Diastolic blood pressure (mm Hg)	86.6 (12.2)
Ejection fraction	
≤ 50%	77 (11%)
≤ 45%	58 (9%)
≤ 40%	38 (6%)
≤ 35%	21 (3%)
Median (range)	60 (10–60)
NT-proBNP (pmol/l)†	35.7 (32.8 to 38.9)
Abnormal ECG‡	197 (30%)
Drug treatment	
Loop diuretics	37 (6%)
Other diuretics	82 (12%)
ACE inhibitor	42 (6%)
Angiotensin II blocker	12 (2%)
β Blocker	30 (5%)
Calcium antagonist	39 (6%)
Nitrates	26 (4%)
Digitalis	25 (4%)
Aspirin	112 (17%)

Data are numbers (%) or mean (SD).

ACE, angiotensin converting enzyme; NT-proBNP, N-terminal pro-brain natriuretic peptide.

*World Health Organization classification of dyspnoea (grade 2, dyspnoea when vacuum cleaning or climbing stairs to the second floor; grade 3, when walking on an even road; grade 4, at minimum exertion; grade 5, orthopnoea; grade 6, at rest).

†Geometric mean concentration and 95% confidence interval.

‡Normal ECG with absence of arrhythmias, ST deviations, Q waves, hypertrophy, and abnormal left ventricular axis according to the Minnesota code.

Diagnosis of systolic heart failure

With the aim of evaluating the diagnostic potential of NT-proBNP in clinical heart failure, subjects were classified as having or not having systolic heart failure. Systolic heart failure was the diagnosis for patients with symptoms of heart failure in the form of dyspnoea or ankle oedema and with objective evidence of heart failure in the form of impaired systolic function by echocardiography (LVEF ≤ 50%). These criteria are consistent with those set out by the European Society of Cardiology.⁹ LVEF ≤ 50% was chosen as the main cut off for LV systolic dysfunction, as we aimed at assessing the diagnostic and prognostic utility of the marker in mild systolic heart failure. However, results with different cut offs (LVEF ≤ 45%, ≤ 40%, and ≤ 35%) are also given. Stratified by these criteria, 623 patients were categorised as normal, whereas 49 (7% of the study population and 64% of patients with LVEF ≤ 50%) met the criteria for systolic heart failure (table 3).

As fig 1 shows, the plasma concentration of NT-proBNP increased with worsening systolic heart failure (symptoms and LVEF ≤ 50%, ≤ 45%, ≤ 40%, and ≤ 35% (heart failure ≤ 50/≤ 45/≤ 40/≤ 35), respectively; $p < 0.0001$).

Potential markers for heart failure ≤ 50 were analysed in a multivariate model with history of hypertension, history of ischaemic heart disease, diabetes, age, sex, heart rate, systolic and diastolic blood pressures, abnormal ECG, and NT-proBNP. Log₁₀ (NT-proBNP) (parameter estimate 1.43, odds ratio 4.17, $p < 0.0001$), abnormal ECG (parameter estimate 1.32, odds ratio 3.73, $p = 0.0007$), and history of ischaemic heart disease (parameter estimate 1.32, odds ratio 3.76, $p = 0.0002$) came out as independent markers.

ROC curves were calculated for the ability of NT-proBNP to diagnose heart failure ≤ 50, ≤ 45, ≤ 40, and ≤ 35. For the diagnosis of heart failure ≤ 40, the following results were obtained: sensitivity/specificity 0.92/0.86, positive predictive value /negative predictive value 0.11/1.00, AUC = 0.94, NT-proBNP = 106.7 pmol/l (fig 2, table 4).

High risk patients

A subgroup of patients at high risk of developing heart failure was defined as those with a history of ischaemic heart disease (angina, previous myocardial infarction, or both), history of hypertension, or diabetes mellitus (all self reported). One or more of these criteria were met by 246 patients (median (range) age 70.6 (51.2–90.8) years, geometric mean (95% confidence interval) NT-proBNP 47.9 (41.4 to 55.4) pmol/l). Of these, 34 patients (14%) had diagnosed heart failure ≤ 50.

A second high risk group of patients aged > 70 years ($n = 294$, median (range) age 78.5 (70.0–91.3) years, geometric mean (95% confidence interval) NT-proBNP 69.5 (61.9–78.0) pmol/l) was defined, in which 36 patients (12%) had diagnosed heart failure ≤ 50.

The diagnostic power of NT-proBNP for systolic heart failure in these high risk groups was evaluated by ROC curve analyses and was, apart from significantly higher NT-proBNP

Detection of LV systolic dysfunction

To evaluate NT-proBNP as a marker for LV systolic dysfunction, ROC curves were calculated for the ability of NT-proBNP to detect LVEF ≤ 50%, ≤ 45%, ≤ 40%, and ≤ 35% (table 2).

Table 2 Diagnostic value of NT-proBNP in detecting left ventricular systolic dysfunction

LVEF cut off	Sensitivity/ specificity	PPV/NPV	AUC	NT-proBNP (pmol/l)*	Diagnoses made per 100 screened	Diagnoses missed per 100 screened	False positives per 100 screened
50% ($n = 77$)	0.70/0.63	0.20/0.94	0.70	41.5	8.02	3.44	32.8
45% ($n = 58$)	0.74/0.64	0.16/0.96	0.73	43.3	6.39	2.24	32.9
40% ($n = 38$)	0.76/0.67	0.12/0.98	0.79	48.9	4.30	1.36	31.1
35% ($n = 21$)	0.76/0.85	0.14/0.99	0.83	100.5	2.38	0.75	14.5

AUC, area under the curve; LVEF, left ventricular ejection fraction; NPV, negative predictive value; PPV, positive predictive value.

*NT-proBNP concentration corresponding to optimal combination of sensitivity and specificity.

Table 3 Baseline characteristics in normal participants and in patients with systolic heart failure

	Normal (n = 623)	Systolic heart failure* (n = 49)	p Value†
Male sex	42%	55%	NS
Median (range) age (years)	67.1 (51.2–91.3)	76.3 (51.8–88.7)	<0.0001
Mean (SD) heart rate (beats/min)	75.2 (13.1)	77.7 (16.3)	NS
Mean (SD) systolic blood pressure (mm Hg)	143 (22.9)	146 (27.0)	NS
Mean (SD) diastolic blood pressure (mm Hg)	86.7 (12.0)	84.7 (14.7)	NS
Median (range) LVEF (%)	60 (15–60)	40 (10–50)	<0.0001
Mean (95% CI) NT-proBNP (pmol/l)‡	32.7 (30.1 to 35.5)	112 (73.1 to 170)	<0.0001

*Defined as symptoms of heart failure and LVEF of $\leq 50\%$.

†p Value for differences between mean values in patients with and without systolic heart failure.

‡Geometric mean concentrations.

cut off concentrations, only slightly inferior to its performance in the undivided population (table 4).

Prognosis

After the examination, patients were followed up for a median (range) of 805 (60–1171) days. Potential independent prognostic markers for total mortality, congestive heart failure admissions, and other cardiac admissions (history of hypertension, history of ischaemic heart disease, diabetes, age, sex, dyspnoea, ankle oedema, heart rate, systolic and diastolic blood pressures, abnormal ECG, LVEF, and NT-proBNP) were evaluated by Cox proportional hazards analyses.

\log_{10} (NT-proBNP) (hazard ratio (HR) 5.70, $p < 0.0001$) and male sex (HR 3.10, $p = 0.004$) were identified as independent markers for mortality. \log_{10} (NT-proBNP) (HR 13.83, $p < 0.0001$), dyspnoea (HR 1.45, $p = 0.003$), and male sex (HR 2.71, $p = 0.03$) came out as independent markers for congestive heart failure admissions. Lastly, \log_{10} (NT-proBNP) (HR 3.69, $p < 0.0001$), abnormal ECG (HR 2.56, $p = 0.003$), and history of ischaemic heart disease (HR 1.90, $p = 0.03$) were identified as independent markers for other cardiac admissions, eliminating LVEF from all prognostic models.

All-cause mortality (26 v 6, $p = 0.0003$) (fig 3), congestive heart failure admissions (18 v 2, $p = 0.0002$) (fig 4), and admissions for other cardiac causes (44 v 13, $p = 0.0001$) (fig 5) were significantly higher for patients with NT-proBNP > 32.5 pmol/l (median study concentration) than for patients with NT-proBNP < 32.5 pmol/l.

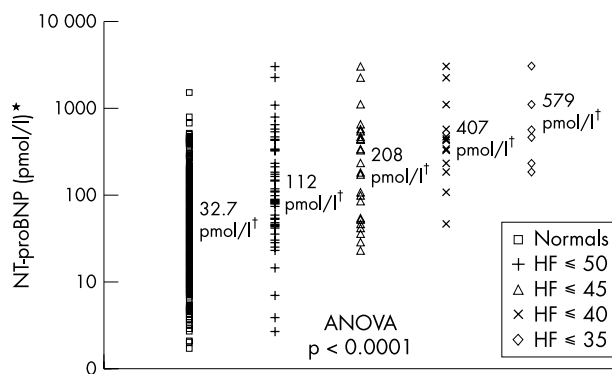


Figure 1 Plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) in normal participants and in patients with symptoms of heart failure (HF) $\leq 50\%$, $\leq 45\%$, $\leq 40\%$, and left ventricular ejection fraction (LVEF) $\leq 50\%$, $\leq 45\%$, $\leq 40\%$, and $\leq 35\%$, respectively. ANOVA, analysis of variance. *Log scale; †geometric mean concentrations.

DISCUSSION

This is the first population based study to confirm that the plasma concentration of NT-proBNP is raised in patients with LV systolic dysfunction and symptoms of heart failure and that NT-proBNP is a strong predictor of death and cardiac morbidity—superior to LVEF evaluated by high quality echocardiography. In addition, we have shown that in a random, age controlled sample of the general population, the plasma concentration of NT-proBNP can detect patients with systolic heart failure, consistent with the European Society of Cardiology criteria,⁹ with a high sensitivity and specificity.

Screening for initial stages of any disease, enabling earlier treatment and, theoretically, a greater reduction in morbidity and mortality, is a valuable medical tool. Screening for heart failure in the population seems to meet all of the well established criteria for a successful individual screening programme.^{22–23} The condition sought should be the precursor of an important health problem, which is certainly the case for heart failure, as it is both common^{3–4} and serious²⁴ and it poses a significant economic burden to society.²⁵ The natural history of the disease has to be well understood, which is also true for heart failure, as many studies have confirmed the eventual progression of myocardial damage of a certain extent to chronic heart failure, often through a phase of asymptomatic, potentially treatable LV dysfunction.^{26–27} The disease should be effectively treatable, which is the case for heart failure, as large scale trials have confirmed the effectiveness of angiotensin converting enzyme inhibitors,⁶ β blockers,⁷ and spironolactone⁸ in increasing the survival of patients with chronic heart failure. Lastly, and fundamental to any screening program, is the availability of a suitable diagnostic test.

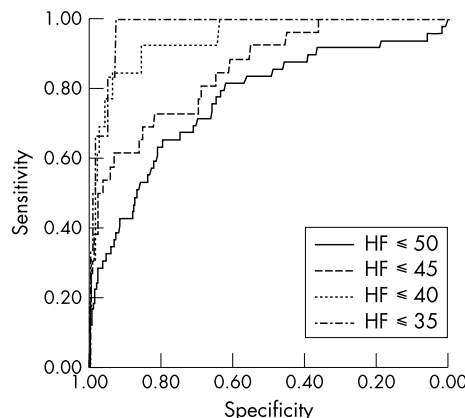


Figure 2 Receiver operating characteristic (ROC) curves for the ability of NT-proBNP to diagnose systolic HF $\leq 50\%$, $\leq 45\%$, $\leq 40\%$, and $\leq 35\%$, respectively, and LVEF $\leq 50\%$, $\leq 45\%$, $\leq 40\%$, and $\leq 35\%$, respectively.

Table 4 Diagnostic value of NT-proBNP in detecting systolic heart failure

	Diagnosis*	SENS/SPEC	PPV/NPV	AUC	NT-proBNP (pmol/l)†	Diagnoses made per 100 screened	Diagnoses missed per 100 screened	False positives per 100 screened
All (n = 672)	HF ≤ 50 (n = 49)	0.65/0.80	0.20/0.97	0.77	72.8	4.74	2.55	18.5
	HF ≤ 40 (n = 13)	0.92/0.86	0.11/1.00	0.94	106.7	1.78	0.15	13.7
Age > 70 years (n = 294)	HF ≤ 50 (n = 36)	0.64/0.74	0.26/0.94	0.74	106.7	7.84	4.41	22.8
	HF ≤ 40 (n = 11)	0.91/0.91	0.29/1.00	0.94	229.0	3.40	0.34	8.66
High risk medical history‡ (n = 246)	HF ≤ 50 (n = 34)	0.68/0.72	0.28/0.93	0.73	72.8	9.40	4.42	24.1
	HF ≤ 40 (n = 9)	0.89/0.80	0.14/0.99	0.90	106.7	3.26	0.40	19.3

*HF ≤ 50/40 indicates patients with symptoms of HF and LVEF ≤ 50/40%.

†NT-proBNP concentration corresponding to optimal combination of sensitivity and specificity.

‡Patients with a history of ischaemic heart disease (angina or previous myocardial infarction), history of hypertension, or diabetes mellitus.

Until now, systolic heart failure has been diagnosed by a combination of a clinical evaluation and some objective measure of LV systolic function. Clinical evaluation is unreliable and inherently incapable of detecting the asymptomatic precursor.²⁸ Echocardiography, the predominant method of evaluating LV systolic function, is both observer dependent and somewhat imprecise, as the technique is most often based on assumptions of LV shape not fulfilled in most patients with LV damage. In addition, although population screening with echocardiography may provide a solution, it would be very labour intensive and probably not cost effective. Clearly, a cheap, simple, and precise biochemical screening option would be more attractive.

In our age controlled sample of the general population, NT-proBNP came out as a powerful diagnostic marker for systolic heart failure with a strength similar to that of other well established screening methods, such as prostate specific antigen for detection of prostate cancer (AUC = 0.94),²⁹ and superior to mammography for breast cancer (AUC = 0.85)³⁰ and Papanicolaou smears for cervical cancer (AUC = 0.70),³¹ suggesting that NT-proBNP is a valid and acceptable test for systolic heart failure in a population screening setting. In addition, NT-proBNP is very stable in plasma and in whole blood and can be stored at room temperature for several days without significant degradation. The test should therefore prove very simple to handle in practice.¹³

Until now, very limited population based data on the diagnostic performance of biochemical markers in heart failure have been published, making it difficult to compare our results with previous studies. However, in one population based study by McDonagh and colleagues,¹⁷ the diagnostic

performance of BNP to detect LVEF ≤ 30% was very similar to our results, yielding an AUC of 0.88 in the undivided general population. In a highly selected group of 106 patients with new symptoms suspected by a general practitioner to be due to heart failure, Cowie and colleagues³² found that BNP identified patients who were subsequently determined to have heart failure with an AUC of 0.96.

Restriction of our analysis to patients at high risk of heart failure, in which the prevalence of undetected systolic heart failure was 14%, compared with 7% in the whole study population, only slightly reduced the diagnostic potential of NT-proBNP, yielding a higher detection rate with little loss in sensitivity. Similar results were found by McDonagh and colleagues,¹⁷ supporting the idea that targeting of high risk patients may be a more efficient population screening approach. This is of course true, as the detection rate would go up; but, on the other hand, some, presumably the younger patients who are probably likely to benefit the most from relevant medication, would risk being missed in the screening. In our study, 13 of 49 (27%) patients with systolic heart failure were younger than 70 years.

Our finding that NT-proBNP was an excellent predictor of all cause mortality and cardiac morbidity is in line with previous results from Richards and colleagues,³³ who, in patients with known ischaemic heart failure and in post-myocardial infarction patients,¹² found the plasma concentration of NT-proBNP to be of prognostic significance. Apart from underscoring the pivotal role of the marker in heart failure, our prognostic findings suggest that initially missing the diagnosis of heart failure in patients with borderline NT-proBNP may not be crucial, as the prognosis of patients with

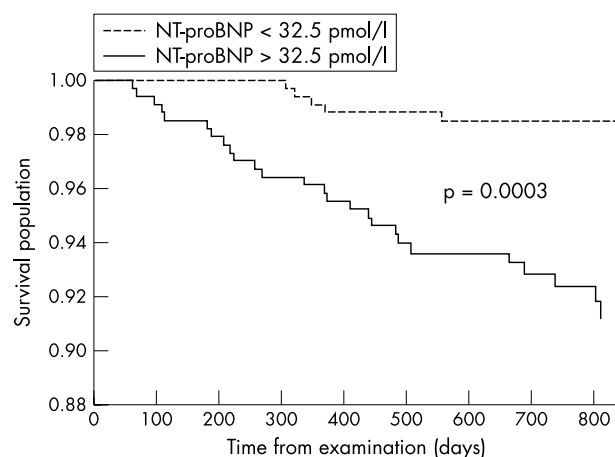


Figure 3 Kaplan-Meier survival curves for patients with NT-proBNP plasma concentrations > 32.5 pmol/l and with NT-proBNP concentrations < 32.5 pmol/l (study median NT-proBNP concentration).

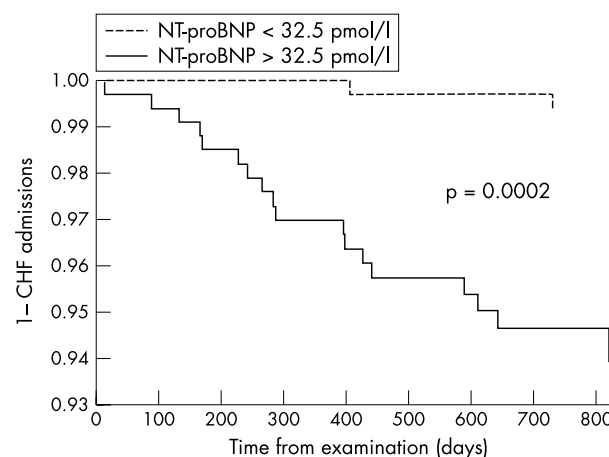


Figure 4 Kaplan-Meier curves for the first admission to hospital for congestive heart failure (CHF) for patients with NT-proBNP plasma concentrations > 32.5 pmol/l and with NT-proBNP concentrations < 32.5 pmol/l (study median NT-proBNP concentration).

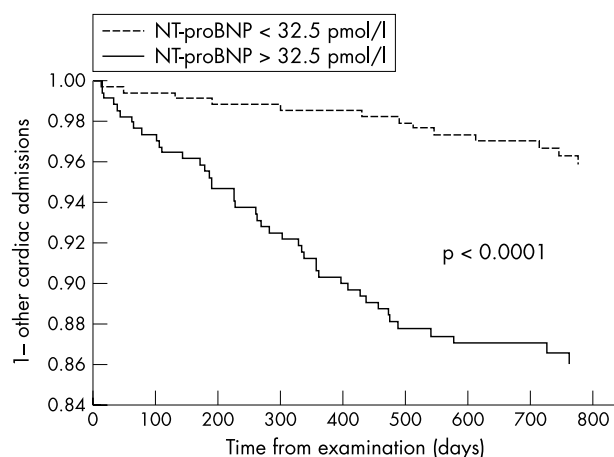


Figure 5 Kaplan-Meier curves for the first admission to hospital for cardiac causes other than CHF for patients with NT-proBNP plasma concentrations > 32.5 pmol/l and with NT-proBNP concentrations < 32.5 pmol/l (study median NT-proBNP concentration).

NT-proBNP below the median is very good, even in the absence of relevant treatment. This view is further supported by the findings of Troughton and colleagues,³⁴ who in patients with known heart failure showed that a reduction in the plasma concentration of NT-proBNP by standard heart failure medication was associated with an improved prognosis.

Study limitations

As shown in the results section, the non-responders were more ill than the participants. This tends to underestimate the true prevalence of heart failure, which means that some patients with severe heart failure have probably not been included in the study, especially among the elderly. This is likely to have given a less favourable result on the utility of the test. The number of events available for assessment of the prognostic utility of NT-proBNP was rather low. Even though the statistical analysis takes this into account, the prognostic data should be interpreted with caution.

Conclusions

Taken together, our results suggest that NT-proBNP may be useful as a screening tool for systolic heart failure in a general population screening setting.

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IMAGES IN CARDIOLOGY

Aortic valve endocarditis causing fatal myocardial infarction caused by ostial coronary artery obliteration

A 43 year old man developed biventricular heart failure over a period of eight weeks following dental extraction. On admission he was found to have severe congestive hepatopathy with profound jaundice, pronounced ascites, and peripheral oedema. Auscultation of the heart revealed a 3/6 holosystolic and a 3/6 diastolic decrescendo murmur, both audible over all precordium. Transthoracic echocardiography (see panels) confirmed moderate to severe aortic regurgitation and the presence of a large vegetation (VEG), located apparently at the downstream side (vegetations typically arise from the upstream side of valve leaflets/cusps) of the right coronary cusp of the aortic valve (parasternal short axis and long axis views show a partly obstructive mass in the aortic root above the right coronary cusp). The patient, at the time unfit for surgical intervention, was treated medically with oral angiotensin converting enzyme inhibition, intravenous antibiotics, diuretics, subcutaneous heparin, and percutaneous ascites drainage. He made a steady recovery clinically before dying suddenly 13 days following hospital admission. Blood cultures had remained sterile throughout. Postmortem examination revealed absence of significant coronary artery disease but presence of a myocardial infarction of the posterior wall of the left ventricle. A large friable vegetation measuring $2.1 \times 1.5 \times 1.0$ cm appeared to occlude the ostium of the left coronary artery. Acute myocardial infarction caused by coronary artery occlusion and/or embolisation is a rare but recognised complication of aortic valve endocarditis. Vegetation size (> 10 mm), extent, mobility, and consistency have been proposed as echocardiographic predictors of systemic embolic events in some but not all studies.

This case highlights the risk of acute myocardial infarction associated with very large aortic valve vegetations and emphasises that the relative risk for embolisation may not dramatically decline with time after initiation of antimicrobial treatment.

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